PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 15451PCT00	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK 03/00592	International filing date *(day/month/year)* 12.09.2003	Priority date *(day/month/year)* 12.09.2002
International Patent Classification (IPC) or both national classification and IPC A61K39/39		
Applicant PHARMEXA A/S, et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.04.2004	17.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Herrero, M Telephone No. +49 89 2399-8542

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00592

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-50 as originally filed

Sequence listings part of the description, Pages

1-12 as originally filed

Claims, Numbers

1-59 filed with telefax on 06.12.2004

Drawings, Sheets

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-44, 56 and 59 with respect to industrial applicability; 18-59 (all partly)

   because:

   ☒ the said international application, or the said claims Nos. 1-44, 56 and 59 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☒ the claims, or said claims Nos. 18-59 (all partly) are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 18-59 (all partly)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-59
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-59
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	45-55, 57, 58
	No:	Claims	

2. Citations and explanations

see separate sheet

SECTION I

6. Additional observations:

6.1 The newly filed Claims 1-59 submitted with telefax of 06.12.04 have their basis in the originally filed application, and therefore do not contravene Art. 34(2)(b) PCT.

6.2 The present preliminary examination report has been established taking into consideration the counterarguments presented in the Applicants' telefax of 06.12.04, in reply to the objections under Arts. 5 and 6 PCT raised in the written opinion dated 07.10.04.

SECTION III

1. Claims 1-44, 56 and 59 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT (i.e. Claims 1-44 and 56: methods of treatment of the human or animal body by therapy and Claim 59: method of transforming cells with a vector of interest insofar as carried out *in vivo*).

   Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. As a consequence of the lack of support and/or sufficiency of disclosure deficiencies within the meaning of Art. 6 PCT and/or Art. 5 PCT which affect the subject-matter encompassed by present Claims 45-47 (corresponding to Claims 49-52 as originally filed), the International Search Report (ISR) has not been established in respect of part of the subject-matter encompassed by present Claims 45-47.

   According to the statements on Form PCT/ISA/210 of the ISR, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely for those parts of the claims related to the compounds mentioned in present Claim 19 (SEQ ID Nos:1-5), the compounds used in the examples (SEQ ID Nos:15-17) and the general idea of the invention, i.e. inducing an immune response against ghrelin, especially by active immunotherapy.

In view of the above statements it is apparent that only a part of the subject-matter encompassed by present Claim 18 (cf Claim 18 as originally filed) and dependent Claims 20-44 (insofar as dependent on present Claims 18-19) has been searched.

Moreover, it is emphasized that insofar as the definition of the subject-matter of present Claims 48-52 (vectors), 53-55 (transformed cells), 57 (composition), 58 (stable cell line) and 59 (method for the preparation of the cell according to any of claims 53-55) eventually relies on the nucleic acid fragment according to present Claim 47, it has to be assumed that all these claims have only been searched in part.

The present International Preliminary Examining Authority (IPEA) agrees with the aforementioned objections set forth in the ISR and notes that claims, or parts of claims, relating to inventions in respect of which no ISR has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). Accordingly the present preliminary examination report has only been established for the subject-matter in respect of which an ISR has been drawn (Rule 70.2(d) PCT).

The applicant is additionally advised that the EPO policy when acting as an IPEA is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

SECTION V

2. CITATIONS AND EXPLANATIONS

2.1 In view of the priority documents pertaining to the present application, the international patent application WO 02/070711 (publication date 12.09.02) cited in the International Search Report under the "P" category, is not to be regarded as state of the art according to Rule 64 (1) PCT as the date of priority of 12.09.02 is validly claimed for the corresponding relevant parts of the instant application.

2.2 The following documents have been considered for the purposes of this report:

D1: WO 01/87335

D2: US 2001/020012
D3: WO 02/066056
D4: WO 95/05849 (cited in the application)

D4 has not been cited in the ISR. A copy of the document has been provided to the Applicants.

2.3 Novelty and inventive step (Art. 33(2) and (3) PCT)

Having regard to the documents cited in the ISR present Claims 1-59 would in principle appear to relate to novel subject-matter and thus to fulfill the requirements of Art. 33(2) PCT.

Moreover, the subject-matter of present Claims 1-59 seems to involve an inventive step, as required by Art. 33(3) PCT, for the following reasons:

The problem to be solved by the present application may be regarded as the provision of novel/improved therapies for the treatment of conditions associated with the metabolic effects of ghrelin.

As noted on page 3, lines 34-36 of the description, the skilled reader can conclude from the relevant findings reported in the state of the art (for instance from the disclosures mentioned on page 3, lines 3-33) that ghrelin does play an important role in obesity and that the need for a marked reduction in ghrelin production in obese patients undergoing diet is essential for (i) loosing weight, i.e. reducing excess body fat, and (ii) subsequently retaining a diet-induced weight loss.

In line with the aforementioned findings the related prior art (e.g. D1 and D2) envisages therapeutic methods for the treatment of obesity and related disorders in a mammal based, for instance, on the administration of a ghrelin neutralizing agent, e.g. an anti-ghrelin antibody (see e.g. page 6, lines 6-8 and 17-26; page 14, lines 1-11 and Claim 6 of D1), or of a ghrelin homologue capable of acting as

an antagonist ligand on the ghrelin receptor (see e.g. Claims 8 and 14 relying on Claims 6-7 of D2).

In contrast to the purposes of the foregoing therapeutic treatments, the application

describes and claims a method for increasing body mass in an animal based on up-regulating autologous ghrelin in the animal by immunizing against autologous ghrelin according to the approach referred to in present Claim 1.

The results discussed on page 6, lines 22-26 and page 35, lines 22-34 bridging over page 36, lines 1-36 and page 37, lines 1-14 of the supporting description (concerning the experimental data presented in Example 1) substantiate the existence of an unexpected physiological effect, namely an increase in body weight associated with the induction of antibodies against autologous ghrelin, obtainable by immunization against several particular ghrelin derivative peptides of the type defined in Claim 1.

Hence, the subject-matter of the claims presently on file seemingly represents a solution to the technical problem posed which cannot be obviously derived from the available prior art. Accordingly, it may be acknowledged the presence of an inventive step associated with said claimed solution (Art. 33(3) PCT).

2.4 Industrial applicability (Art. 33(4) PCT)

For the assessment of the present Claims 1-44, 56 and 59 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2.5 Further comments

(i) In view of the explanations provided in the Applicants' reply dated 06.12.04 and the related statements in the supporting description (see page 36, lines 15-17) it

is has to be considered that preservation of all B-cell epitopes of mature ghrelin in the immunogenic ghrelin variants to be employed according to the approach defined in Claim 1 is a structural feature essential to the definition of those immunogenic constructs capable of inducing an immune response which causes

the surprising effect of providing a weight gain.

Since independent Claim 1 does not contain this characterizing structural feature it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the performance of the invention.

The same deficiency (Art. 6 PCT/Rule 6.3(b) PCT) affects present independent Claims 45, 46, 47, 48, 53, 57, 58 and 59.

(ii) The experimental results provided in Example 1 substantiate the existence of a(n) surprising/unexpected physiological effect associated with the administration of certain immunogenic variants of ghrelin (i.e. peptides 3-5 corresponding to SEQ ID Nos:15-17).

Nevertheless, in line with the observations in item (i) above, it would appear that the surprising/unexpected physiological effect demonstrated in Example 1 does not constitute a general phenomenon which could be expected to take place as a consequence of the administration of any possible immunogenic ghrelin construct falling under the corresponding definitions given in present Claims 1-3.

Thus, the subject-matter presently claimed is not adequately supported by the description as required by Article 6 PCT, as its scope is broader than justified by the description and drawings.

It is additionally noted that Example 2 merely proposes to carry out part of the claimed invention, in order to identify further ghrelin derived constructs which could perform the pursued effect of increasing body mass recited in Claim 1.

(iii) The lack of technical information concerning a possible generalization of the unexpected increase in body weight mediated by the induction of antibodies against autologous ghrelin referred to above (e.g. being positively associated with

the administration of certain types/groups of ghrelin derivative peptides), highlights that the subject-matter of Claims 1-3 is insufficiently disclosed over the wide scope of the claims, contrary to Art. 5 PCT.

(iv) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor are these documents identified therein.

(v) See that page 1, line 15 reads "emancipation".